REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the amendments to the claims and remarks presented herewith, which place the application into condition for allowance, or in better condition for appeal.

Status of the Claims and Formal Matters

Claims 1-4, 13, 16-24, 26, and 27 are currently pending in this application. Claims 8-12, 14, and 25 have been withdrawn, and Claims 5-7 and 15 have been cancelled. Applicants reserve the right to claim withdrawn and/or cancelled subject matter in co-pending applications. By this paper, Claims 1, 2, and 20 have been amended, without prejudice. No new matter has been introduced by these amendments. Support for the amended recitations can be found throughout the specification, for example, at page 4, line 10; page 4, lines 18-22; page 5, lines 10-13; page 11, line 25; page 15, lines 12-24; page 25, beginning at line 25 and continuing to page 26, line 21; as well as page 27, lines 12-13; and page 37, beginning at line 28 and continuing to page 38, line 1.

Rejections under 35 U.S.C. §103(a)

Claims 1-4, 13, 18-24 and 26 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Morin et al, U.S. Patent No. 6,610,839 in view of Chin et al., U.S. Patent No. 6,197,599. The Office Action at pages 2 and 3 alleges that Morin discloses the present invention substantially as claimed, i.e., Morin allegedly teaches the use of a fusion protein system to isolate specific proteins and peptides. Morin does not teach that the bound proteins are in an array, however, Chin allegedly teaches that protein immobilized on a solid support can be immobilized in an array, or a specific position. The Office Action contends that it would have been obvious to one of skill in the art to form the immobilized proteins as described by Morin in the form of an array as taught by Chin for the advantage of identifying a protein based on its position and studying a wide variety of proteins in a single experiment for convenience. This rejection is respectfully traversed.

The provisions of MPEP §2143 set forth three requirements to establish a *prima facie* case of obviousness. First, there must be some teaching, suggestion, or motivation in the cited

references to modify or combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference(s) must teach or suggest all of the claim limitations. Applicants respectfully submit that the teachings of Morin and Chin, whether considered alone or in combination, do not teach or suggest all of the instant claim limitations. Furthermore, there is no motivation to combine or modify the teachings of Morin and Chin.

The present invention relates to, *inter alia*, a method of generating a protein array from a plurality of target DNA sequences. An advantageous feature of the instant invention is that a plurality of DNA sequences can each be individually tagged with a marker moiety to facilitate the direct immobilization of the resultant tagged amino acid sequences to a solid support, which allows for purification and immobilization of the tagged amino acid sequences in a single step. This allows one of ordinary skill in the art to tag a plurality of DNA sequences and subsequently purify and immobilize the tagged expression products in a single step, via the marker tag to a solid support in a spatially defined format. Applicants refer to page 8 of the Office Action, where it is stated that Applicants' previous arguments were not deemed persuasive because Claim 1 allegedly does not require a single step that purifies and immobilizes affinity-tagged proteins, nor does Claim 1 require that the proteins are immobilized via the tag. For the reasons supplied herein and in view of the amendments to the claims, it is respectfully submitted that the instantly claimed subject matter is not rendered obvious by the teachings of the cited references.

Morin relates to isolated nucleic acids that encode the catalytic subunit of human telomerase (hTRT). The Office Action refers to col. 43, lines 27-34 of Morin, which allegedly discloses fusion protein systems that can be used to facilitate efficient production and isolation of hTRT proteins or peptides that can be immobilized via non-hTRT sequences, such as polyhistidine tracts and antibody epitopes. However, Morin does not teach or disclose tagging a plurality of target DNA sequences. Morin only teaches insertion of a tag onto one particular DNA sequence, hTRT. Furthermore, Morin does not teach or disclose the purification and immobilization of the one particular tagged sequence or a plurality of tagged sequences to a solid support in a single step, wherein the proteins are directly attached to the solid support via the marker moiety. Morin simply teaches that tagged hTRT sequences can be bound to a solid support to separate the fusion protein "from unbound components" (see Morin, col. 43, lines 29-

34). Notably, Morin is silent as to the purification and immobilization of tagged proteins in a single step, as well as their immobilization to a solid support in a spatially-defined format.

Chin does not cure the deficiencies of Morin, because Chin does not teach or disclose methods for making a protein array by purifying and immobilizing a plurality of tagged amino acid sequences directly to a solid support via a marker tag moiety in a single step. In fact, Chin teaches away from the instantly claimed invention because Chin describes at col. 4, lines 18-26, that agents such as proteins are bound to antibodies, and the antibodies are then attached to a solid support. Chin further teaches at col. 5, lines 39-42 that "[w]hen a protein is captured by its antibody immobilized on an array, other proteins may also be tethered to the same position due to protein-protein interaction" (emphasis added), which indicates that the Chin arrays require proteins that are indirectly immobilized to a solid support via an antibody linker. Furthermore, Chin exemplifies only arrays that immobilize proteins via protein-protein interactions with an antibody. The skilled artisan, relying upon Morin and Chin, would not arrive at the instant invention, because Morin teaches an individual fusion protein that is not purified and immobilized in a single step to a solid support via the marker tag in a spatially defined format. While Chin may teach a plurality of proteins as alleged in the Office Action, Chin does not teach or suggest any specific method of obtaining the proteins on the array. "Obvious to try", e.g., varying all parameters or attempting each of numerous possible choices until one possibly arrived at a successful result, where the prior art gives no direction as to which of many possible choices is likely to be successful, is not the standard under which a proper §103(a) rejection can be based (MPEP §2145(X)(B)). Whether considered alone or in combination, the teachings of Morin and Chin do not render the instant invention obvious, because Morin and Chin are deficient as to tagging a plurality of target DNA sequences and purifying and immobilizing, in a single step, the tagged expression products directly to a solid support via the marker tag in a spatially defined format.

For the foregoing reasons, it is respectfully submitted that a rejection under §103(a) by Morin in view of Chin cannot stand. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Claims 16 and 17 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Morin in view of Chin, and further in view of Ben-Bassat et al., U.S. Patent No. 4,865,974.

The Office Action at page 4 alleges that although Morin teaches that the hTRT stop codon is removed and replaced by vector sequences encoding for the Myc epitope and the His6 reporter tag, Morin does not specifically disclose the steps for removing and replacing the DNA sequences. Ben-Bassat allegedly teaches that the steps of digesting, annealing and ligating are well known in the art for removing and replacing DNA sequences. The Office Action contends that it would have been obvious to one of ordinary skill in the art to use the steps of digestion, annealing, and ligation as taught by Ben-Bassat for the steps of removing and replacing the DNA sequences in the method taught by Morin. Applicants respectfully traverse this rejection.

For the reasons stated above, Morin considered alone or in combination with Chin does not result in the instantly claimed invention because both Morin and Chin are silent as to methods of tagging a plurality of target DNA sequences to generate an array of tagged proteins that are purified and immobilized directly to a solid support via the tag, in a single step and in a spatially defined format. Ben-Bassat does not cure the defects of Morin and Chin because Ben-Bassat merely provides a method of removing N-terminal methionines from amino acid sequences using an E. coli Met-aminopeptidase. While Ben-Bassat may disclose methods for digesting, annealing, and ligating DNA sequences, Ben-Bassat is completely silent as to purifying and immobilizing tagged proteins directly to a solid support via the tag moiety, whether or not it is achieved in a single step. Consequently, reconsideration and withdrawal of the rejection under §103(a) over Morin in view of Chin in view of Ben-Bassat is respectfully requested.

Claim 24 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Morin in view of Chin and further in view of Orr et al., U.S. Patent No. 5,741,645 and Nielsen et al., U.S. Patent No. 6,350,853. The Office Action states at page 5 that Morin in view of Chin discloses the invention substantially as claimed except for two markers, one immediately following a start codon and one immediately preceding a stop codon. Orr allegedly discloses this limitation by teaching the use of two flanking markers for the advantage of isolating region-specific DNA markers. Nielsen allegedly teaches a marker sequence immediately following a start codon. The Office Action argues that it would have been obvious to one of skill in the art to provide two flanking markers as taught by Orr in the method taught by Morin because Orr allegedly teaches the advantage of isolating region-specific DNA markers. Further, the Office

Action contends that it would have been obvious to provide the second marker immediately following a start codon as taught by Nielsen as a known location for inserting a marker. Applicants respectfully traverse this rejection.

As provided above, Applicants respectfully disagree with the rejection under §103(a), because the teachings of Morin in combination with Chin does not result in the present invention as claimed. Morin and Chin, considered alone or together, do not describe a method of making a protein array by tagging a plurality of target DNA sequences, and subsequently purifying and immobilizing the tagged expression products directly to a solid support via the tag moiety, in a single step and in a spatially defined format. Orr does not cure the deficiencies of Morin and Chin, because Orr relates to an isolated 1.2 Mb region of human chromosome 6 that contains a highly polymorphic CAG repeat region and which correlates to the spinocerebellar ataxia type 1 locus (SCA1). The Office Action refers to col. 16, lines 40-44 of Orr, which discloses that the SCA1 locus isolated from a human-hamster cell line "retains markers immediately flanking D6S89". These markers are disclosed by Orr at col. 4, lines 60-64 as "dinucleotide repeat markers used in the genetic analysis of SCA1 families." These dinucleotide repeats are naturally-occurring sequences in the chromosome that are used for identifying and locating portions of a chromosome containing a particular sequence of interest, wherein the length of the particular sequence can be megabases or longer in length. Orr is silent as to inserting a marker DNA sequence in frame immediately following a start codon of each of a plurality of target DNA sequences in a cDNA library, or immediately preceding a stop codon of each of the plurality of target DNA sequences to result in tagged, expressed proteins for the purpose of making a protein array. Orr merely describes the presence of naturally-occurring dinucleotide repeats that are present on either side of a large 1.2 Mb stretch of chromosome 6 that allows one of skill in the art to identify approximately where SCA1 locus is located. These naturally-occurring dinucleotide repeats are present in the chromosome and are not inserted.

Nielsen describes peptide nucleic acids having a polyamide backbone which are conjugated to lipophilic groups and are incorporated into liposomes. The Office Action refers to col. 33, lines 23-25 that allegedly describes a marker sequence immediately following a start codon, but the marker sequence disclosed by Nielsen is actually a short sequence containing a fluorescein moiety conjugated to a D-lysine residue on a short nucleobase sequence that binds to

a region of the chloramphenical acetyltransferase gene for the purpose of inhibiting translation of CAT *in vitro*. Nielsen does not teach, disclose, or suggest that the sequence referred to by the Office Action is used to insert a tag immediately after the start codon of a plurality of target DNA sequences in a cDNA library, or immediately before the stop codon of a plurality of target DNA sequences, for the purpose of making tagged proteins on an array.

Applicants respectfully submit that due to the lack of motivation to combine any of the Morin, Chin, Orr and Nielsen references, the Examiner is using impermissible hindsight to pick and choose discrete features from the prior art that are believed to result in the instant invention. In view of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the rejection under §103(a) over Morin in view of Chin in view of Orr in view of Nielsen.

Claim 27 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Morin in view of Chin and further in view of Stanley et al, U.S. Patent No. 5,861,250 and Little et al., U.S. Patent No. 6,387,628. The Office Action alleges that Morin in view of Chin discloses the invention substantially as claimed, except for disclosure that the marker moiety provides a high-affinity attachment to the solid support. Stanley allegedly teaches that a molecule may be labeled with histidine for linking to a solid phase, and also teaches that subsequent detection methods may be performed after capture to the solid support. Stanley discloses that the captured molecule is a nucleic acid, however Little allegedly teaches that histidine tags on proteins specifically interact with nickel ions on a column to separate the protein from a reaction mixture. The Office Action argues that it would have been obvious to the skilled artisan to provide a solid support with chelatable nickel ions as taught by Stanley and Little as the solid support in the disclosure of Morin in view of Chin. This rejection is respectfully traversed.

For reasons detailed above, Applicants respectfully state that Morin and Chin do not render the instant invention obvious because Morin and Chin do not teach or disclose all of the claim limitations. Further, Morin and Chin are deficient in that they do not teach, disclose, suggest, or provide any motivation for a method of making a protein array by tagging a plurality of DNA sequences and purifying and immobilizing the tagged proteins directly to a solid support in a single step. The teachings of Stanley and Little, whether considered alone or together, do not remedy the deficiencies of Morin and Chin.

Stanley relates to methods for detecting a specific nucleic acid sequence contained in a nucleic acid sample using, for example, nucleic acid sequences that can be labeled with a moiety suitable for linking to a solid phase, such as histidine or biotin. However, Stanley only provides the skilled artisan with guidance as to methods of identifying a nucleic acid of interest from a sample containing a population of nucleic acids by hybridizing the nucleic acid of interest to a nucleic acid analogue that can be labeled. Stanley does not teach or disclose a protein array containing tagged proteins expressed from a plurality of tagged target nucleic acid sequences, wherein the tagged proteins are purified and immobilized via the marker tag in a single step to a solid support in a spatially defined format as provided by the instant invention.

Little relates to processes for determining the identity of a target polypeptide using mass spectrometry. The Office Action alleges that Little, at col. 59, lines 56-61, teaches that histidine tags on proteins specifically interact with nickel ions on a column to separate the protein from a reaction mixture. Little does not cure the defects of Morin in view of Chin, because Little does not teach or suggest a method of generating a protein array by tagging a plurality of target DNA sequences and subsequently purifying and immobilizing the tagged proteins directly to a solid support in a single step. Little merely teaches that a target polypeptide having a tag, such as histidine, can be isolated by binding to a solid phase, after which it is subjected to mass spectrometry.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejections under §103(a) over Morin in view of Chin in view of Stanley in view of Little.

CONCLUSION

Favorable action on the merits is respectfully requested. If any discussion regarding this Response is desired, the Examiner is respectfully urged to contact the undersigned at the number given below, and is assured of full cooperation in progressing the application to allowance.

Respectfully submitted,

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